Introduction. Biopharmaceutics and Pharmacokinetics

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1.1 Introduction

The terms biopharmaceutics and pharmacokinetics describe two relatively young pharmaceutical sciences. Both have attracted more and more interest in the last decades, as the medical and pharmaceutical communities recognized their effective and potential contributions to design rational dosing recommendations and exploit our therapeutic arsenal in the best possible manner (Hochhaus et al. 2000). The significance of these areas of knowledge has been further enhanced by the attention on the relationship between drug levels in different body compartments and the correspondent pharmacological effects and by the opportunity of predicting in vivo performance of a drug product (typically reflected by plasma drug concentrations or rate and amount of drug absorbed) from in vitro performance (Emami 2006). What is more, last generation pharmaceutical carriers (e.g., pharmaceutical nanocarriers) have recently been introduced which, for the first time in history, could directly participate in and impact on the fate of a drug within the body, providing specific

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(or targeted) distribution and modifying elimination kinetics (Talevi and Castro 2017). Such innovative drug products defy some well-established biopharmaceutical and pharmacokinetic concepts, which should be adapted or expanded to encompass the advances in pharmaceutical technologies. The propagation of complex drug delivery systems explains that today, more than ever, it is necessary that a wider audience gains at least basic biopharmaceutics and pharmacokinetics knowledge, in order to understand the behavior of such systems, assist in their design, and optimize their use.

First of all, what do we mean by biopharmaceutics and pharmacokinetics?

► Definition

Biopharmaceutics: Barbour and Lipper (2008) have noted that, by introducing the prefix *bio* to the word *pharmaceutics*, it follows that biopharmaceutics study the interdependence of biological aspects of the living organism (i.e., the patient) and the physical/chemical principles that govern the preparation and behavior of the medicinal agent and/or the drug product (Barbour and Lipper 2008). The discipline examines the interrelationship of the physical/chemical properties of the drug, the dosage form in which the drug is delivered, and the route of administration, on the rate and extent of systemic drug absorption (Shargel et al. 2012).

Pharmacokinetics: Pharmacokinetics is a branch of pharmacology that studies, both mathematically and descriptively, how the body affects a drug after administration, through the processes of absorption, distribution, metabolism, and excretion. It has been observed, in a colloquial manner, that pharmacokinetics deals with "what a biosystem does to a compound," that is, with everything that happens to drug molecules within the body aside from the pharmacodynamics events (Testa and Krämer 2006). In his seminal works, Torsten Teorell, who is often regarded as the father of modern pharmacokinetics, observed that the clinicians were often interested in some aspects of drug action (e.g., their specific mechanism of action), while little attention was paid to kinetics, that is, the time relation of drug action. Accordingly, he decided to derive "general mathematical relations from which it is possible, at least for practical purposes, to describe the kinetics of distribution of substances in the body" (Paalzow 1995).

Some authors assimilate both biopharmaceutics and pharmacokinetics into a single discipline. While for conventional drug delivery systems it could make sense to consider both disciplines separately (with the focus of biopharmaceutics in drug release from dosage forms and the focus of pharmacokinetics on those processes happening from absorption onward), such distinction may get blurry when considering last generation drug delivery systems, for which drug release could occur during or after drug distribution.

Conceived either as separate disciplines or as one, all in all biopharmaceutics and pharmacokinetics study what we succinctly call LADME processes, an acronym that refers to the processes of liberation (i.e., drug release from the dosage form), absorption, distribution, metabolism, and excretion. Briefly, *absorption* refers to the drug movement from the absorption site to systemic circulation, *distribution*

represents the reversible transfer of drug molecules to the extravascular compartment, *metabolism* represents drug elimination due to biotransformation of drug molecules through enzyme-catalyzed chemical reactions, and *excretion* denotes the physical removal of the drug from the body. ADME processes will be studied in separate chapters of this volume. Metabolism and excretion can be jointly regarded as elimination, whereas distribution, metabolism, and excretion are together referred sometimes as drug disposition.

It is worth differentiating the epistemic object of biopharmaceutics from *biopharmaceuticals*. Biopharmaceuticals (also known as *biological medical products*, *biodrugs,* or, simply, *biological*s) are pharmaceutical drug products manufactured in, extracted from, or semi-synthesized from biological sources, including vaccines, blood, blood components, gene therapies, tissues, recombinant therapeutic proteins, and living cells used in cell therapy. They can be composed of sugars, proteins, nucleic acids, or complex combinations of these substances or may be living cells or tissues. Biologicals, as any other drug product, may be studied by biopharmaceutics and pharmacokinetics (in fact, a whole chapter of this volume will focus on the kinetics of this type of medications). The procedures to obtain and characterize biologicals fall within the realm of biotechnology and molecular biology.

1.2 Some Practical Definitions: The Notion of Bioavailability

For the best understanding of this and subsequent chapters by those readers who are not familiarized with pharmacology and pharmaceutical glossary, we will next provide some general definitions of terms which would be frequently used throughout this volume.

► **Definition** Active pharmaceutical ingredient: The biologically active component of a drug product, that is, the component directly responsible for the pharmacological response. It is also usually referred as *drug*. Some drug products include more than one active pharmaceutical ingredient. Such substances can be used in the diagnosis, cure, mitigation, treatment, or prevention of disease.

Drug product: Through appropriate manufacturing processes, active pharmaceutical ingredients are combined with inactive pharmaceutical ingredients called excipients, which compose the pharmaceutical vehicle, pharmaceutical carrier, or drug delivery system. Closely related to the dosage form concept (physical form in which a drug product is produced and dispensed, e.g., tablet, capsule, syrup, etc.), excipients may contribute to different aspects of the drug products, such as enhancing physical/chemical or microbial stability, improving organoleptic properties, bulking up solid formulations that contain potent active ingredients in small amounts, enhancing drug dissolution or absorption, etc. The pharmaceutical carrier does not possess intrinsic pharmacological activity, though its composition and manufacturing process impact on drug release and absorption and, thus, in drug pharmacokinetics. Some last generation pharmaceutical carriers may also influence drug distribution and elimination.

Biophase: The effect site of a drug. Physical region (environment) in which the drug target is located.

Systemic treatment or systemic medication: A pharmacological treatment in which the therapeutic agent (the drug) reaches its site of action through the bloodstream. We will consider that a drug molecule has reached systemic circulation once it has left the left ventricle of the heart at least once, that is, once it has reached the aorta.

Topical medication: A medication that is locally applied to the particular place on or in the body where it is intended to elicit its action. Many topical medications are applied directly to the skin. Topical medications may also be inhalational or applied to the surface of tissues other than the skin, such as eye drops applied to the conjunctiva or ear drops placed in the ear.

Therapeutic window: Also known as therapeutic range, it refers to the range of drug concentrations in a bodily fluid (usually, plasma) that provides safe and effective therapy. The lower bound of the therapeutic range is called minimum effective concentration (MEC), whereas the upper bound is called minimum toxic concentration (MTC). Below the lowest concentration of the window, it is likely that the drug will fail to work. If the drug concentration climbs above the therapeutic window, a detrimental intensification of the drug's intended (*on-target*) and unintended (*off-target*) actions will occur. Tabulated limits of the therapeutic window often come from population studies. However, to some extent, each individual has, at a given time point, a unique therapeutic window for each drug, since there are interindividual (and also intraindividual!) variability in drug sensitivity. Drugs with narrow therapeutic windows present small differences between therapeutic and toxic doses. For those drugs, therapeutic drug monitoring (the clinical practice of measuring specific drugs in body fluids at designated intervals) is often performed, to guarantee that the drug achieves the desired concentrations in the patient. When initiating drug therapy with such therapeutic agent, the physician may find it useful to measure the plasma drug concentration and tailor the dosage to the individual, "personalizing" the therapeutic intervention.

Drug target: A biomolecule with which the drug specifically interacts to elicit its therapeutic response. Most drug targets are proteins, though some correspond to other types of biomolecules (e.g., DNA, RNA).

Bioavailability: Bioavailability refers to the extent and rate at which the drug reaches its site of action. As the determination of drug levels in the site of action is not feasible in some cases (for instance, the reader may imagine how invasive would be to measure drug levels in the central nervous system), bioavailability assessment in the site of action is often replaced by measuring systemic bioavailability, i.e., *the extent and rate at which the drug reaches systemic circulation*. This is more convenient, since drug levels are more frequently quantified in serum or plasma. Plasma drug levels have a direct relationship with those in the site of action. This does not mean that drug levels across different organs will be uniform and identical

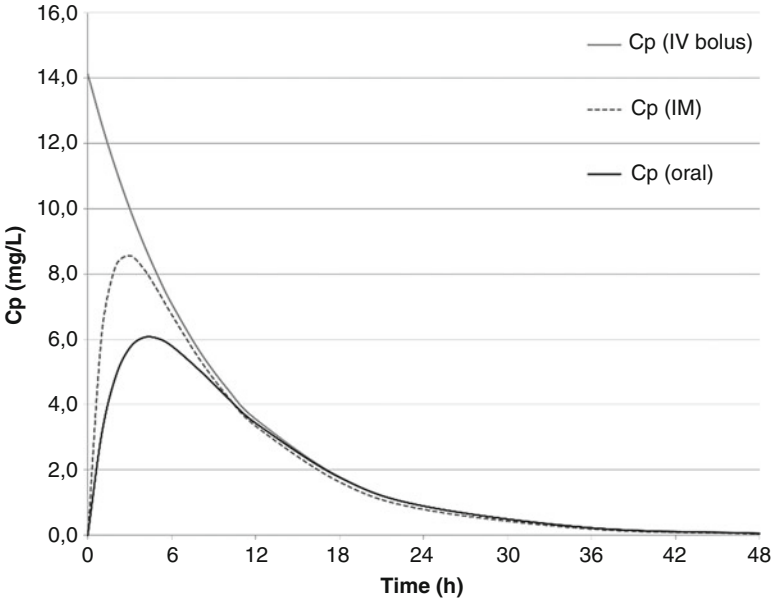

Fig. 1.1 Plasma concentration-time profiles for different routes of administration. Assume that the area under the curve is the same for the three profiles, thus indicating that the total amount of drug that has been absorbed is the same in all cases. Obviously, the kinetic aspect of bioavailability differs in every case. The IV administration implies immediate systemic bioavailability of the entire administered dose; in the other extreme, oral administration implies the slowest absorption, and thus the lowest bioavailability

to those in plasma; it means that, the higher the drug levels in plasma, the higher the drug levels in extravascular tissues. It is important to underline that, although we will frequently focus on drug bioavailability, measuring bioavailability of other types of compounds (e.g., toxins, drug metabolites) could occasionally be of interest. Bioavailability assessment is typically performed from drug plasma concentration-time profiles.

If we take the previous definition of bioavailability into consideration, we will observe that bioavailability has quantitative (extent) and kinetic (rate) components. Figure 1.1 shows a hypothetical situation in which the same dose of a given drug has been administered through different routes of administration (intravenous, intramuscular, oral). Even if, as in the example, the quantitative aspect of bioavailability was the same (as reflected in identical areas under the curve for the three profiles), the kinetic aspect of bioavailability will considerably vary for different administration routes (as reflected by the time at which the drug reaches its maximum plasma concentration). The moment at which the drug levels surpass the MEC and the time period during which the drug levels remain within the therapeutic window will be different in each occasion.

1.3 The Relationship Between Biopharmaceutics and Pharmacokinetics and the Pharmacological Response

Generally speaking, a pharmacologic response will take place when drug molecules interact in a specific manner with drug target molecules. Whereas it is common to speak of the drug target as *receptor*, strictly speaking not all the drug targets correspond to the receptor category. The usually specific recognition event between the drug and the drug target has been classically explained through the key and lock analogy (although now we know that (a) neither the drug nor the target are rigid entities; and (b) considering a systems biology perspective, drug responses can hardly be always explained by a single and punctual interaction event, but by the diversity of events triggered by the interaction of the drug with bodily elements). Speaking in very general terms (more detailed and comprehensive information could be found in a pharmacology textbook), drugs often work by blocking the interaction of a drug target with an endogenous ligand or by inducing a conformational change in the drug target that results in a pharmacologic response.

From the previous comments, it follows that the magnitude of the pharmacological effect will essentially depend on two factors: on the one hand, the number of drug molecules that, at a given moment, are interacting (binding) with the correspondent target copies and, on the other hand, how favorable is (thermodynamically speaking) such interaction. The larger the affinity of the drug for its target, the higher the intrinsic potency of the drug. Note that a maximal response is expected if, at a given moment, all the available copies of the target are occupied by drug molecules (saturated system). Also note that the living system may resort to different strategies to terminate or compensate the action of the drug (e.g., inactivating the drug target, upregulating or downregulating the drug target).

It is interesting to highlight that *the encounter between a drug molecule and a target molecule is a probabilistic event depending on the collision probability between both partners of the drug-target complex. It thus depends on the number of drug molecules neighboring the molecular target and also on the number of copies of the drug target neighboring the drug molecules*.

It is important to meditate on the statement in italics. If we think about it, it explains the relevance of biopharmaceutics and pharmacokinetics. The intensity of the pharmacological response not only depends on the intrinsic potency of the drug but also on how many drug molecules occupy, at a given time point, drug target molecules. This, in turn, directly depends on how many drug molecules are available to the target molecules in the site of action. Even if a drug has a high intrinsic potency, if it does not have access to the biophase in sufficient amount to occupy a pharmacologically relevant proportion of the drug target copies, there will not be pharmacological response.

1.4 The Free Drug Hypothesis

The free drug hypothesis (also called "free drug theory" or "free drug principle" by many authors) provides a conceptual framework to formalize the previous discussion and understand, in subsequent chapters, many issues related to drug distribution and drug elimination mechanisms. It is widely applied in drug discovery and development to establish pharmacokinetic-pharmacodynamic relationships, to predict the therapeutically relevant dose and to monitor drug levels in clinical studies. The hypothesis can be summarized in two prepositions (Smith et al. 2010):

(a) The free drug concentrations at both sides of a biological barrier would be the same if the distribution pseudo-equilibrium (steady state) has been achieved.
(b) The free drug is the species that exerts pharmacological activity (only the collision of free drug with the target is likely to contribute to binding).

The drug concentration in the biophase determines the magnitude of the pharmacological response (at least until maximal response has been achieved). Numerous studies have demonstrated that the average free drug concentration that is present in vivo at the mean efficacious dose is in good agreement with the in vitro potency (see, for instance, Troke et al. (1990) and Yamada et al. (2007)).

But what does free drug mean? In physiologic media, some drug molecules will reversibly bind to components in plasma (primarily, proteins) and in tissues, whereas others will be free (i.e., unbound, interacting with no other things than solvent molecules). Free drug molecules will diffuse across biological barriers much more rapidly than their bound counterparts.

There are many exceptions to the free drug hypothesis (Trainor 2007; Smith et al. 2010), for instance, a drug that has low passive permeability, so that the diffusion into a cell or deep compartment is slow relative to changes in plasma concentration. A major category of exceptions to the hypothesis involves drugs which are substrates for drug transporters. Exceptions to the second part of the hypothesis include drugs whose action involves multiple mechanisms and the activation of target-mediated events and drugs that bind to their targets with a very slow rate of dissociation from the complex, which will sustain receptor occupancy and exert pharmacological effect long after free drug levels have dropped off.

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Further Reading

This introductory chapter has discussed some pharmacological concepts in a very brief and general manner. The reader is directed to pharmacology textbooks for a deeper insight into pharmacology basis. Chapter 4 of the volume *Pharmacology: Principles and Practice* (by Hacker et al, Elsevier, 2009) would be an excellent place to find more on ligand binding and tissue response